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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,505	01/25/2002	Roger Y. Tsien	02307E-151530US	7832

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EXAMINER	
ROBINSON, HOPE A	
ART UNIT	**PAPER NUMBER**
1652	

MAIL DATE	DELIVERY MODE
11/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/057,505	TSIEN ET AL.	
	Examiner	Art Unit	
	HOPE A. ROBINSON	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *79-84 and 91-99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *79-84 and 91-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/21/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Applicant's response filed to the Office Action mailed on February 20, 2008 on July 21, 2008 is acknowledged.

Claim Disposition

2 . Claims 79-84 and 91-99 are pending and are under examination.

Claim Objection

3. Claim 79 is objected to because of the following informalities:

Claim 79 is objected to because of the following: "moiety is excited.;" where an extraneous period appears.

Correction is required.

Maintained-Claim Rejections - 35 USC ء 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 79-81, 91-94, 97 and 99 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a donor fluorescent

protein moiety and an acceptor fluorescent moiety contained in SEQ ID NO:2 with specific mutations to SEQ ID NO:2 at the positions listed in for example claim 79 and the disclosure in U.S. Patent No. 5,981,200, (for example, wherein the linker is a peptide moiety that does not emit light to excite the donor fluorescent protein moiety), does not reasonably provide enablement for mutations to the donor and acceptor moieties that are "85% identical to SEQ ID NO:2" that may not produce FRET or similar variability in the linker moiety. In addition, the claims read on any linker and the specification is not enabled for any linker as the linker moiety may refer to a single amino acid or a group or any linker with a protease recognition site for any protease. While the specification is enabled for linkers that are not fluorescent, is not enabled for linkers that are fluorescent. Further, the specification while enabled for linkers about 5-50 amino acids (see page 2 of the specification) is not enabled for linkers with the lengths encompassed in the breath of the claims. For example claim 87 recites "comprises between 5 and 50 amino acids, which means that the open language "comprises" extends the length in the N or terminus.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: quantity of experimentation necessary; amount of direction or guidance presented; presence or

absence of working examples; nature of the invention; state of the prior art relative skill of those in the art; predictability or unpredictability of the art and breadth of the claims, each of which will be discussed below.

The claims are directed to a tandem fluorescent protein construct, comprising a donor fluorescent protein moiety, an acceptor fluorescent protein moiety and a linker moiety that couples the donor and acceptor moieties and wherein the donor and acceptor moieties exhibit FRET when the donor moiety is excited by radiation, characterized in that the linker moiety comprises a protease cleavage recognition site, wherein cleavage of the linker by a protease results in a change in FRET between the donor and acceptor moieties. The specification on page 8, line 12-15 appears to describe linkers as encompassing in scope those molecules that can be fluorescent in the same manner as the donor and acceptor moieties (in defining the "linker moiety" as a "radical" in the same manner as the fluorescent protein moieties). The specification only provides guidance for the use of linkers as a non-fluorescent moiety that provides at least the appropriate degree of separation between donor and acceptor moieties. There is no guidance to use the linker in any other manner, and the effect of having an additional fluorescent moiety between the donor and acceptor would have unpredictable consequences on resonance transfer, which as taught on page 12 of the instant specification is extremely sensitive to the degree of separation between donor and acceptor. One of skill in the art would have to engage in undue experimentation to provide linkers with the properties encompassed by the claims given these factors. The claims are also directed to donor and acceptor moieties comprising SEQ ID NO:2

comprising several amino acid substitutions. Therefore the claims encompass undefined structures or multiple fluorescent moieties for which the specification is not enabled. To construct and test the many protein fragments encompassed in the claim to see the desired properties are retained would require undue experimentation.

Additionally, the specification fails to describe or provide any identifying characteristics or properties for the "other mutations" encompassed in the open claim language or provide data to demonstrate that function is retained or that the protein moieties exhibit FRET. Therefore, while it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. For example, Heim et al. (PNAS, vol. 91, pages 12501-04, 1994) disclose that a mutated DNA was sequenced and found to contain five amino acid substitutions, only one of which was found to be critical, Tyr66His, in the center of the chromophore. Heim et al. also disclose further site directed mutagenesis and noted that there was tolerance of the substitutions made, however, some mutants were weakly fluorescent (page 12504). The substitutions contemplated by the instant invention is greater than that proposed in the art, hence the specification should provide guidance as to what portion of the sequence is conserved and define the "other mutations" encompassed in the "comprising" language.

In addition, the specification on page 20, line 31 discloses that the optimal distance between the donor and acceptor sites is between about 1nm to about 10nm for

the claimed resonance energy transfer to be useful. However, the "fluorescent protein moieties" encompass fluorescent peptide fragments of the intact fluorescent proteins, the distance between donor and acceptor may be about as short as the length of the linker. On page 20 of the specification it is stated that the length of the linker moiety is chosen to optimize both FRET and the kinetics and specificity of enzymatic cleavage. Thus, if the linker is too short, the protein moieties may sterically interfere with each other's folding or with the ability of the cleavage enzyme to attack the linker. However, the claims broadly encompass linkers that are greater than 5-50 amino acids or 1-10nm in length which is not supported by the instant specification that discloses that linker length is a critical parameter required for the tandem conjugates to work and that linker lengths beyond about 1-10nm would unpredictably result in interference with polypeptide folding, enzyme cleavage, insufficient resonance transfer, or linker cleavage specificity. Moreover, the claims recite two fluorescent protein moieties said to be linked to one another via a linker moiety, the specification does not provide guidance as to covalent binding occurring via cyclization and oxidation of amino acids of the donor and acceptor protein moieties, or via any other methods considered to produce the "coupling" of the donor and acceptor protein moieties. No information is provided as to how the individual fluorescent moieties are to be isolated and ultimately linked to one another via any linking moiety. Thus, absent adequate guidance/direction regarding for example, the linker length, based on the breath of the claims, the undefined structures encompassed by the claims, the nature of the invention and the unpredictability of the

linker as recited in the claims, a skilled artisan would not be able to practice the claimed invention commensurate in scope with the claims.

In view of the foregoing, one of skill in the art would require guidance, beyond that provided in the instant specification, in order to make the claimed tandem fluorescent protein in a manner that reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

Maintained- Basis For Non-Statutory Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 79-84 and 91-99 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 43-44 of U.S. Patent No. 6,803,188. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in each are directed to tandem fluorescent protein constructs comprising a donor fluorescent moiety, an acceptor fluorescent moiety linked by a linker moiety, wherein the donor and acceptor moieties exhibit fluorescence resonance energy transfer (FRET) when said donor is excited and wherein the linker moiety has a protease cleavage recognition site. Both sets of claims recite substitutions that can occur to the donor and acceptor moieties which comprise an *Aequorea* fluorescent protein with respect to SEQ ID NO:2. Note that the modifications contemplated in the patent are encompassed in the instant application and therefore the limitations in the instant application are considered obvious in light of the patented claims; the claims of the patent are generic to the instant claims. Therefore, the claims of the patent and the instant application claims are an obvious variation of each other.

Response to Arguments

7. The response filed has been considered. Note that the Obvious-type double patenting rejection remains as not terminal disclaimer was provided with the amendment. Applicant's arguments pertaining to the written description rejections are noted but are moot as the rejections have been withdrawn based on the arguments presented and newly revised written description guidelines. Note that the rejections under 35 U.S.C. 112, first paragraph, enablement remains for the reasons stated above and herein.

Regarding the rejection under 35 U.S.C. 112, first paragraph enablement, applicant state that the claims clearly set forth the requirement "wherein said donor fluorescent protein moiety and said acceptor fluorescent protein moiety exhibit fluorescent resonance energy transfer when said donor fluorescent protein moiety is excited". This argument is not persuasive as said statement does not endow function and the recited 85% encompasses a lot of variability in the protein's structure which can definitely affect the protein's function. Applicants also argue that some inoperative embodiments can be present in the claims. This argument is not persuasive because the claim language is overly broad. As previously stated, the art sets forth that a third of single amino acid changes would completely inactivate the average protein and the more substitutions made the more probability that the protein will be inactivated. Thus, this gives the sense of what one of skill in the art can expect when a claim embraces fragments with up to 10, 20, 30, 40 or more amino acid changes and how many mutants one of skill in the art can test in such an endeavor (see Guo et al., PNAS, vol. 101,

no.25, pages 9205-9210, 2004). Thus, undue experimentation would be required and the variability encompassed in the claims is not routine in the art. Again, the issue at hand is the breath of the claims in view of the art and guidance provided in the specification. The breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record, is the issue at hand. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "…scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art…". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)*. Thus, the rejection remains.

Conclusion

8. No claims are allowable.

9. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed, Ph.D., can be reached at (571) 272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Hope A. Robinson/

Primary Examiner, Art Unit 1652